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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/707,980	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *11/8/2007*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 10/10/2007.

The amendment filed 10/10/2007 is acknowledged and has been entered.

Claims 69-72 are currently pending in the application and are addressed herein.

1. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure.

Support cannot be found for the phrase "an RNA equivalent of (a)" as indicated in claim 69. Since support for the new limitations indicated above could not be found, a rejection of the indicated claims, as well as all claims depending therefrom, are properly rejected under 35 U.S.C. § 112, first paragraph.

Furthermore, claims 69-72 are also rejected under 35 U.S.C. 112, first paragraph because the claims appear to encompass sequences, specifically "RNA equivalents" which are different from the disclosed sequences, but which have not been adequately described in the specification.

It is noted that the specification does not appear to define the term "RNA equivalent". Therefore, given the broadest reasonable interpretation, the claims encompass anything that may be considered an "RNA equivalent" of an isolated nucleic acid consisting of 19-140 nucleotides of SEQ ID NO: 142700, including non-RNA nucleic acids. Therefore, the claims encompass a

genus of molecules which is indeterminate in size, but which could be extremely large considering every possible "RNA equivalent" encompassed by the claims. The specification only appears to disclose SEQ ID NOs: 142700, 140670, 140732, 2 and 9, with respect to the claimed genus. Thus, applicant has express possession of only the 5 specific DNA sequences and the 5 specific RNA sequences which they encode, but not every "RNA equivalent" encompassed by the claims.

The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common element or attributes of the sequences are disclosed. No structural limitations or requirements which provide guidance on the identification of sequences which meet the functional limitations is provided.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that:

> "In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d

1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that: "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acid sequences encompassed by the claims, other than those expressly indicated. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

In the instant application, only the specifically identified SEQ ID NO and the specific RNAs which they encode are adequately described.

Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 69-72 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or, alternatively, a well established utility.

The claims are drawn to isolated nucleic acid sequences. A review of the specification, which is over 8,4000 pages long, finds general assertions and statements that the present invention relates to a group of bioinformatically detectable novel genes, which Applicant refers to as "genomic address messenger" or "GAM" genes, which are believed to be related to the micro RNA (miRNA) group of genes.

The specification teaches that Micro RNAs (miRNAs), are short ~22nt non-coding regulatory RNA oligonucleotides, found in a wide range of species, believed to function as specific gene translation repressors, sometimes involved in cell-differentiation.

The specification makes general statements that the bioinformatically detectable sequences, GAMs, and the miRNAs they may encode may have utility for regulating target genes and possibly for treating disease.

However, the specification provides no direct or indirect evidence for any specific, substantial, or credible utility of the instantly claimed RNAs encoded by SEQ ID NO:142700 (or an RNA equivalent). There is no disclosure indicating or suggesting that SEQ ID NO:142700 has itself ever been isolated or examined in any way, nor any evidence that the claimed RNA has, in fact, been isolated or prepared or studied or examined under any conditions. Any asserted utility for the claimed sequences appears to be merely speculation based on "bioinformatics,"

homology, and secondary structure predictions suggesting that the encoded RNAs are miRNAs because they have a miRNA-like hairpin structure and some degree of sequence homology to some unidentified target sequence. On this basis, and since other miRNAs are known to have gene expression modulating properties, Applicant appears to be asserting that the bioinformatically detectable sequences, or GAMs, such as the RNAs encoded by SEQ ID NO:142700 also have utility.

However, that utility has not been clearly defined, nor does the prior art search of SEQ ID NO:142700 provide any substantial evidence to show that the sequences have a credible utility.

Applicant has not shown, and there is no evidence in the prior art to suggest, that the nucleic acids now claimed are expressed in any cell whatsoever. Indeed, the asserted utility and target gene of this and thousands of other miRNA-like sequences appears to be based purely on bioinformatic methods for predicting RNA folding and potential gene targets.

Krutzfeldt et al. (2006) *Nature Genetics* 38:514-519 state that, in general, the basis for these types of prediction programs is the degree of sequence complementarity between a miRNA and a target UTR, including the presence of a consecutive string of base pairs at the 5′ end of the miRNA known as a 'seed' or 'nucleus', and the cross-species conservation of this binding site. On average, 200 genes are predicted to be regulated by a single miRNA. The authors further state that reviewing the data provided by these algorithms determining candidate targets uncovers the entire gamut of gene categories, such as transcription factors, protein kinases, vesicular trafficking molecules and membrane receptors, suggesting that there is no apparent bias towards one particular function.

Accordingly, while the ability to predict hairpin-like structures and potential gene targets from genomic sequence information appears to be within the state of the art, Krutzfeldt et al. teach that validating the true biological function of any predicted miRNA sequence requires analyzing miRNA expression patterns, as well as testing the effects of miRNA overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*.

Thus, while these methods, too, are within the level of skill in the art, Applicant has presented no evidence that any of these validation techniques have, in fact, been carried out with regard to the instantly claimed sequences. That is, no evidence can be found verifying or even suggesting that the sequences encompassed by the claims, including SEQ ID NO:142700, RNA equivalents, etc., actually gives rise to miRNAs in any cell or organism.

The specification generally asserts that a utility of the novel oligonucleotides of the present invention is detection of GAM oligonucleotides and of GR (Genomic Record) polynucleotides—that diagnosis of expression of oligonucleotides of the present invention may be useful for research purposes, in order to further understand the connection between the novel oligonucleotides of the present invention and disease and disease diagnosis and prevention purposes, and for monitoring disease progress.

However, none of these asserted uses meet the three-pronged requirement of 35 U.S.C. § 101 regarding utility, namely, that the asserted utility be credible, specific and substantial.

Neither the instant specification nor the prior art presents any evidence that instant SEQ ID NO:142700, much less the claimed RNA equivalents thereof have any specific biological function. No evidence or information is found either in the specification or the prior art linking SEQ ID NO:142700 or its RNA with the modulation of any bacterial or mammalian gene or with

the conditions that render cells or hosts susceptible to any disease or disorder, for example. No convincing evidence is found teaching any biological function for SEQ ID NO:142700 at all. In fact, no evidence is found suggesting or stating that the RNAs encoded by SEQ ID NO:142700 have been made, isolated, cloned, detected, expressed, or even analyzed in any living cell *in vitro* or *in vivo*.

In summary, no biological or biochemical function has been assigned to the claimed sequences, apart from the general assertions that it, like the thousands of other sequences described in the sequence listing, may correspond to an miRNA and have some direct or indirect relation to human biology and/or cell function.

Thus, the proposed utility of the sequences as therapeutic targets or agents, research tools, material resources for preparing diagnostic probes, vectors, and systems, are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acid sequences.

Brenner v. Manson, 148 U.S.P.Q. 689 (U.S. 1966)

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> ...a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Thus, the specification does not teach a specific, substantial, or credible utility for claimed sequences. No evidence been presented showing or suggesting that any small RNAs are

actually expressed by SEQ ID NO:142700 in any cell, and, if so, what function these sequences perform.

Claims 69-72 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or, alternatively, a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to Arguments

2. Applicant's arguments filed 6/11/2007 have been fully considered.

With respect to the rejection of claims under 35 USC 112, first paragraph, Applicants argue that the written description requirement is satisfied if the specification describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that Applicant had possession of the claimed subject matter. Applicant submits that SEQ ID NOs: 142700, 140670, and 140732 are GR Precursor DNA sequences (see instant paragraph 0288) and the specification furthers discloses these GR Precursor DNAs encodes a GR Precursor RNAs. Applicant submits that one of ordinary skill would immediately conclude Applicant was also in possession of an RNA equivalent of this sequence according to these teachings.

In response, it is acknowledged that the specification has disclosed that SEQ ID NOs: 142700, 140670, and 140732, and thus provides adequate description of those specific sequences and the specific RNAs which they encode. However, the claims are not limited to these specific

sequences. Rather, the claims encompass any sequence which could be considered an "RNA equivalent" of any of these sequences. The specification does not particularly define the term "RNA equivalent". Therefore, given the broadest reasonable interpretation, the claims are not limited to the indicated SEQ ID Nos and the specific RNA sequences which they encode. Instead, the claims encompass these sequences ad well as any "RNA equivalent" thereof, which could include non-RNA molecules. Therefore, Applicant's argument is not persuasive with respect to the rejection as it now stands.

Wit respect to the rejection of claims under 35 USC 101 and 112, first paragraph, as it applies to the rejection as it now stands, Applicant argue that an asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Applicant submits that the Examiner has not considered the asserted utility as discussed above for using the claimed nucleic acids for modulating expression of specific mRNA targets. Applicant contends that the proper inquiry is instead whether one of ordinary skill in the art would believe that the claimed nucleic acids maybe used to modulate expression of the specific mRNA targets. Applicants assert that paragraph 0265 of the specification discloses that the mRNA targets of the claimed nucleic acids were identified as being consistent with the free energy and spatial structure of target binding sites of known miRNAs and the method as described in paragraph 0265 for identifying target binding sites of miRNAs is based upon studies at the time of filing demonstrating that miRNAs bind to sites in

target mRNAs as disclosed in references which are all cited. Applicants argue that in view of the asserted utilities being consistent with the general understanding of miRNAs and their target binding sites at the time of filing, one of ordinary skill in the art would believe that each claimed nucleic acid would bind its respective target binding sites.

In response, it is acknowledged that an asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Furthermore, the asserted utility of using the claimed nucleic acids for modulating expression of specific mRNA targets has been considered and the disclosure of paragraph 0265 has been fully considered. However, considering the teaching of Krutzfeldt et al. (see above) validating the true biological function of any predicted miRNA sequence requires analyzing miRNA expression patterns, as well as testing the effects of miRNA overexpression and underexpression under different conditions in living cells *in vitro* and *in vivo*. Therefore, based on the teaching of the prior art, further experimentation is necessary in order to determine if the sequences encompassed by the claims encode functional miRNAs. That is, based on the evidence of record, it cannot be said that it is more likely than not that the claimed sequences encode (or are themselves) sequences which can inhibit expression of a target sequence.

Therefore, Applicants arguments, as they pertain to the rejections as they now stand, are not persuasive.

Conclusion

3. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner
AU 1635